Pioneering a New Era of GPCR Drug Discovery

Corporate Presentation

April 2026

Nasdaq: SEPN

Forward-Looking Statements

This presentation contains express or implied forward-looking statements of Septerna, Inc. (the "Company," "we," or "our") within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. All statements other than statements of historical facts contained in this presentation, including statements regarding our business strategy, plans, estimated R&D program milestones and objectives of management are forward-looking statements. Such forward-looking statements include, but are not limited to, statements regarding: the continued advancement of SEP-479 in clinical development, including the anticipated availability of Phase 1 clinical study data in late 2026 or early 2027; the continued advancement of SEP-631, including the plan to initiate a Phase 2b clinical study in chronic spontaneous urticaria in the second half of 2026 subject to the successful completion of long-term preclinical toxicology studies and regulatory filings; the role of MRGPRX2 in mast cell-driven diseases; the ability of preclinical or Phase 1 safety and efficacy observations to successfully translate into positive clinical outcomes; the timing, progress and results of conducting our research and development programs, including our plans to advance the TSHR research program; the intended and potential benefits of the collaboration with Novo Nordisk, including our ability to jointly discover, develop and commercialize multiple potential oral small molecule therapies for obesity, type 2 diabetes, and other cardiometabolic diseases and the potential resulting milestones and royalties (if any); our ability to demonstrate, and the timing of, preclinical proof-of-concept *in vivo* and *ex vivo* for multiple programs; the potential of our proprietary Native Complex Platform®; the size and growth potential of the markets for our current and future product candidates; our expectations regarding strategic plans for our business, product candidates, and technology; the scope of protection we are able to establish and maintain for intellectual property rights covering our Native Complex Platform® and our product candidates; our ability to maintain existing collaborations and to identify and enter into future license agreements and collaborations; and the accuracy of our estimates regarding expenses and capital requirements, including our expected cash runway at least into 2029. Such forward-looking statements reflect the current views of the Company and are subject to known and unknown risks and other factors, which are, in some cases, beyond the Company's control. Risks that contribute to the uncertain nature of the forward-looking statements include those risks and uncertainties set forth in the section titled "Risk Factors" in our most recent Annual Report on Form 10-K for the year ended December 31, 2025, as well as any subsequent filings with the Securities and Exchange Commission.

Certain information in this presentation (including market data and statistical information) and statements made orally during this presentation are the good faith estimates of management and have been obtained from various sources (including third-party sources such as independent industry publications, governmental publications, and reports by market research firms), and we do not guarantee the accuracy or completeness of such information.

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Septerna: Pioneering a New Era of GPCR Drug Discovery with Oral Small Molecules

Native Complex Platform® designed to unlock the full potential of GPCR therapies

- Iterative structure-based drug design to rapidly optimize and validate programs in animal models

Portfolio strategy to drive value creation

- Validated targets + early clinical readouts + multi-billion $ market opportunities

Well-capitalized

- Cash runway expected to support operating plans at least into 2029

Lead Programs

SEP-479 PTH1R Agonist: Potential first-in-class oral small molecule for hypoparathyroidism; Phase 1 in healthy volunteers initiated with SAD/MAD data anticipated in late 2026 or early 2027

SEP-631 MRGPRX2 NAM: Pipeline-in-a-product opportunity for mast cell-driven diseases; Phase 1 SAD/MAD demonstrated robust PD with QD dosing; targeting initiation of Phase 2 trial in CSU in 2H 2026

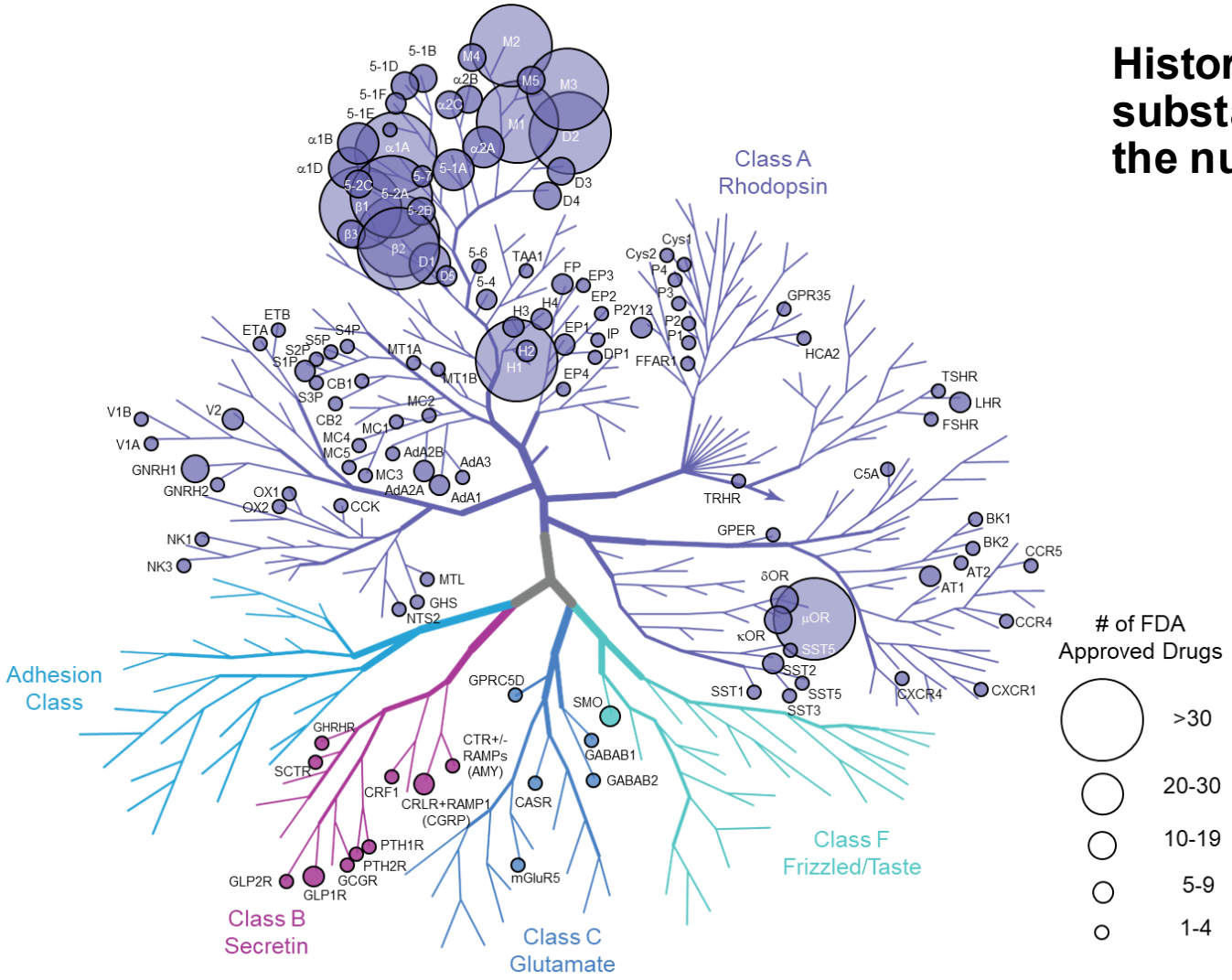
Discovery Stage

TSHR NAM: Potential disease-modifying treatment for Graves' disease and TED; progressing multiple lead compounds toward development candidate selection

Incretin Receptor Agonists: Potential multi-billion $ collaboration with Novo Nordisk for oral small molecules for metabolic diseases

GPCR: G protein-coupled receptor; NAM: negative allosteric modulator; TED: thyroid eye disease; CSU: chronic spontaneous urticaria

GPCR Drug Discovery Success Has Been Highly Concentrated to a Small Fraction of GPCRs



Historically productive target class, yet substantial untapped opportunity to expand the number of druggable GPCRs

~1/3 of all FDA-approved drugs (~500 approved products) target GPCRs

>70% of GPCR drugs target 6 small subfamilies of GPCRs

~75% of potential GPCR targets remain undrugged

Our focus: Unlocking difficult-to-drug GPCRs with our Native Complex Platform®

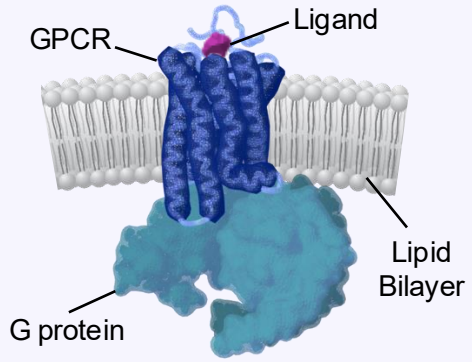
Proprietary Native Complex Platform®

Today's GPCR Drug Discovery Challenge

- Several new small molecule drug discovery technologies have largely been inaccessible to GPCRs
- Inability to isolate fully functional GPCR proteins significantly limits use of modern discovery tools

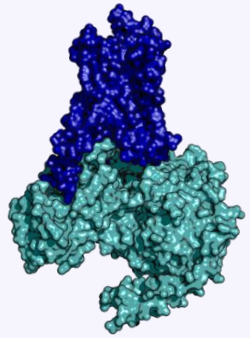
Native Complex Platform® : Industrialized Workflows to Unlock Difficult-to-Drug GPCRs

Native Complexes



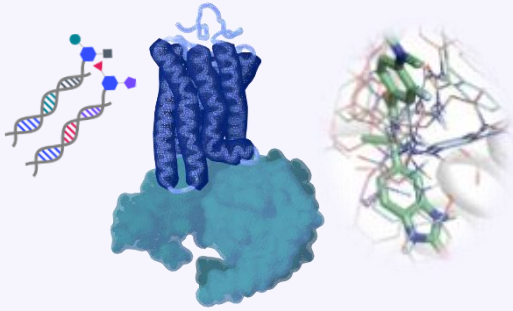
Retain GPCR natural structure, function, and dynamics

High-Resolution GPCR Structures



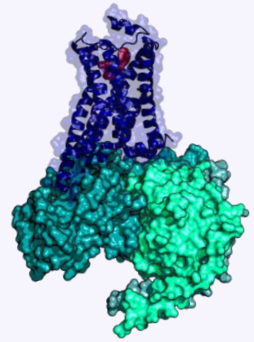
Novel binding pockets and new insights into GPCR modulation

Technologies to Screen Billions of Compounds



Discovery of new leads with relevant modes of action

Structure-Based Drug Design & Optimization



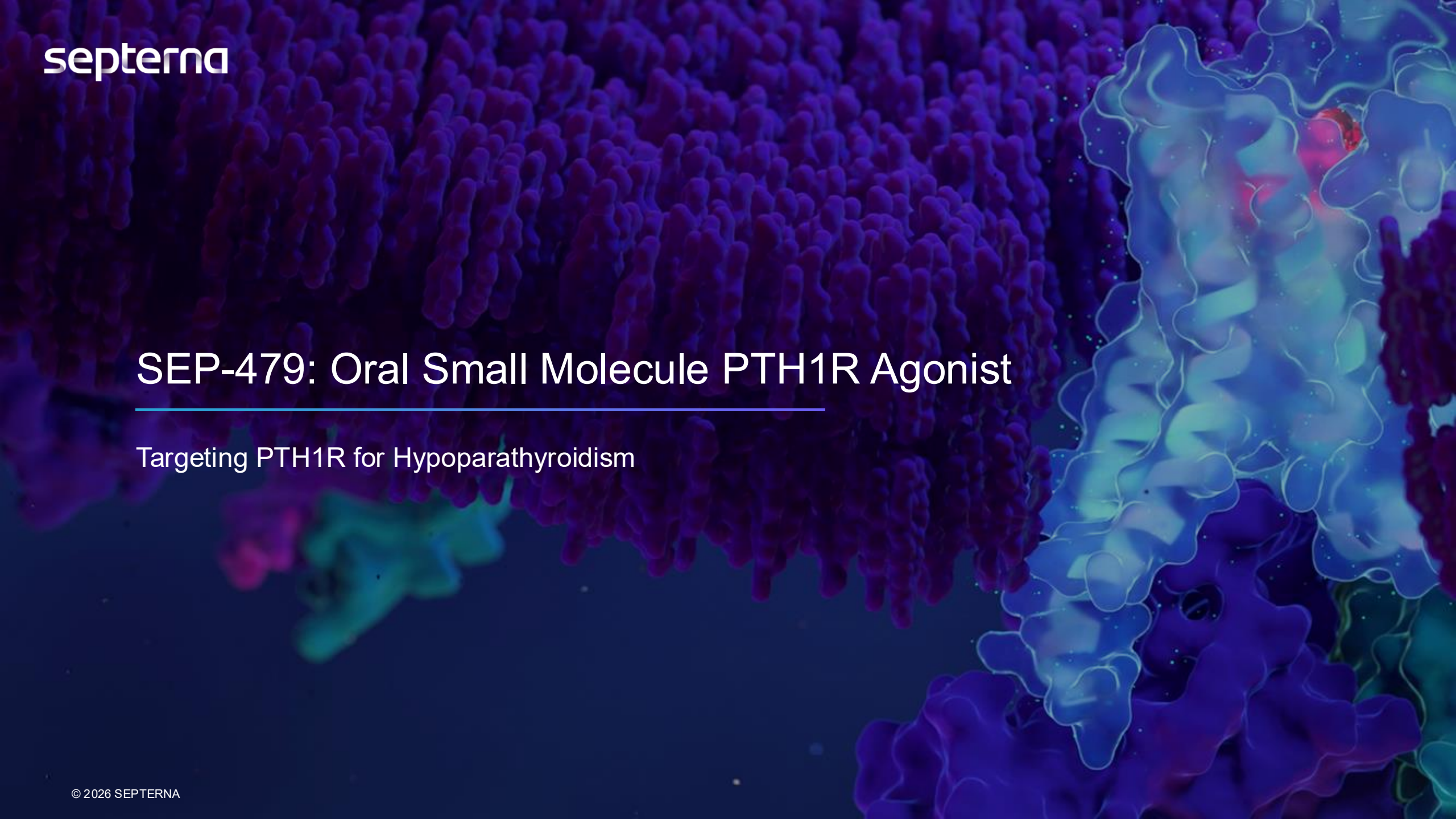
<1 year from initiation of med chem to activity in animal models for each program to date

Advancing a Deep Portfolio of Oral Small Molecule GPCR-Targeted Programs

Wholly-Owned Programs		Development Status			
Program / Target Mode of Action	Therapeutic Area Indications / US Patient Population	Discovery	IND-enabling	Phase 1	Phase 2
SEP-479 (PTH1R) Agonist	Endocrinology Hypoparathyroidism: ~70k				Anticipate Phase 1 data in late 2026 or early 2027
SEP-631 (MRGPRX2) Negative Allosteric Modulator	Immunology and Inflammation CSU: ~1.5mm Other mast cell diseases				Phase 2 initiation * anticipated in 2H 2026
TSHR Program Negative Allosteric Modulator	Endocrinology Graves' disease: ~2mm Thyroid eye disease: ~1mm				
Research Areas: Neurology, Women's Health, Cardiovascular Disease and Respiratory Disease					

Partnered Programs		Partner
Metabolic Programs GLP-1R, GIPR, GCGR + Undisclosed	Obesity and Other Cardiometabolic Diseases	novo nordisk®
Undisclosed	Undisclosed	VERTEX

* Pending successful completion of regulatory submissions



SEP-479: Oral Small Molecule PTH1R Agonist

Targeting PTH1R for Hypoparathyroidism

Hypoparathyroidism: Significant Unmet Need for an Oral PTH Replacement

Hypoparathyroidism: Low PTH leads to low blood calcium

- ~70K patients in US; ~140K patients in EU

Challenging patient symptoms

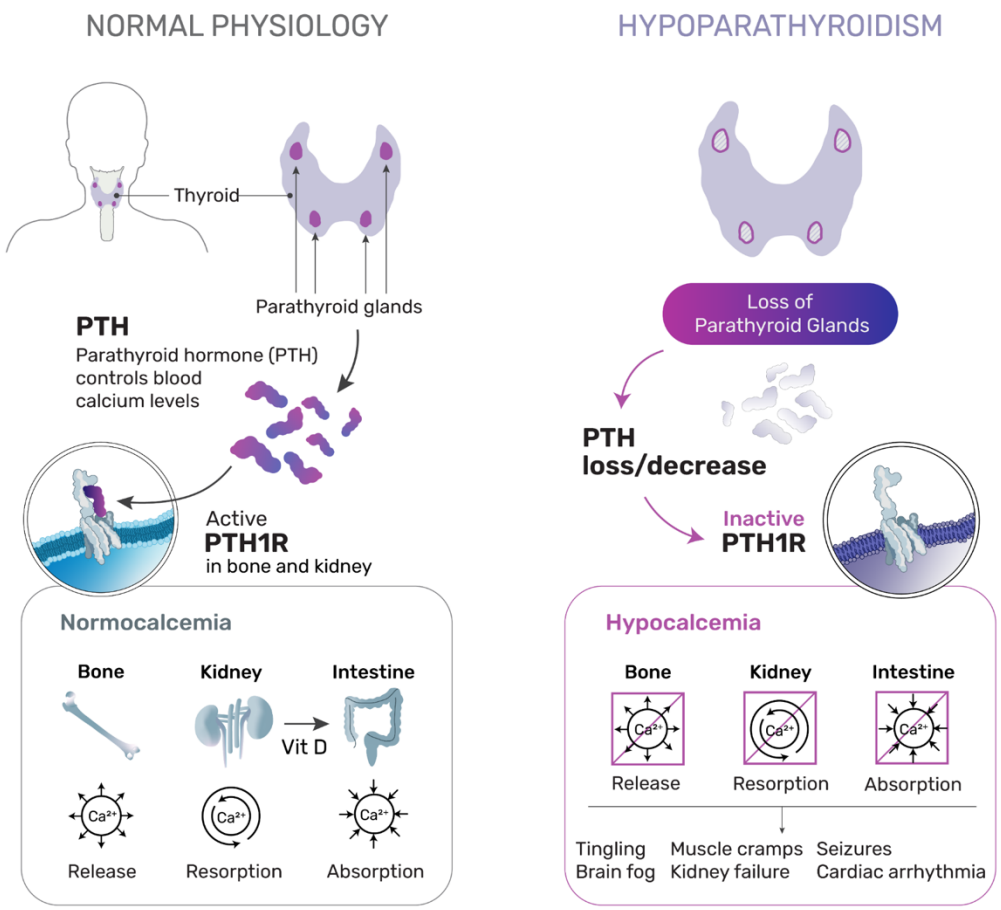
- Muscle cramps, tingling, brain fog
- Life-threatening complications: cardiac arrhythmias, seizures

Standard-of-care limitations

- Calcium supplements (high doses several times per day) and Vitamin D do not fully resolve symptoms and lead to complications including calcifications and renal impairment
- Approved injectable PTH therapy will require life-long daily injections

Our Strategy: Functionally replace PTH with oral small molecule PTH1R agonist to normalize serum calcium

PTH: Master Regulator of Blood Calcium

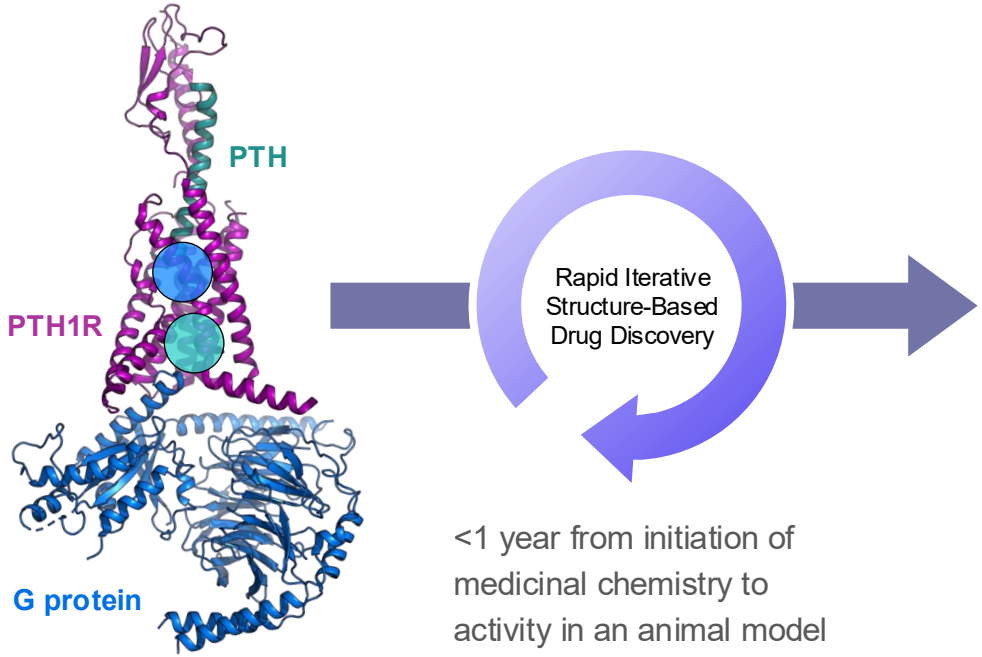


PTH: Parathyroid Hormone

SEP-479: Discovered with Native Complex Platform™ as Potent Oral PTH1R Agonist for Hypoparathyroidism

Native Complex Hit Identification and Structure-Based Optimization

Multiple PTH1R agonists with distinct binding sites identified and optimized in parallel to candidate quality molecules



<1 year from initiation of medicinal chemistry to activity in an animal model

SEP-479: Clinical Candidate

- Potent oral small molecule PTH1R agonist
- Demonstrated comparable effects to PTH peptides in cell-based assays and in vivo models
- Normalized serum calcium in preclinical rat surgical model of hypoparathyroidism
- Monkey PK/PD study demonstrated robust decreases in endogenous PTH and increases in serum calcium
- Excellent pharmaceutical properties; projected to achieve full-day HypoPT control with QD dosing
- Generally well tolerated in GLP toxicology studies

Phase 1 in healthy volunteers is in progress

SEP-479: A Potent PTH1R Agonist Normalized Serum Calcium and Phosphate in Rat Hypoparathyroidism Model

Rat surgical model of hypoparathyroidism

Rat

↓ Surgery to remove parathyroid glands

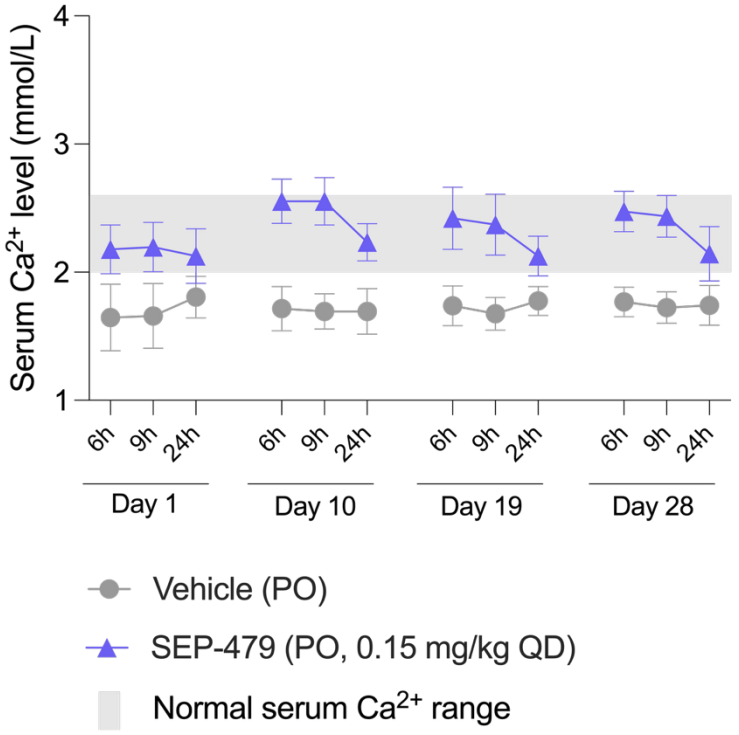
Decreased serum calcium (hypocalcemia)

↓ Oral small molecule PTH1R agonist

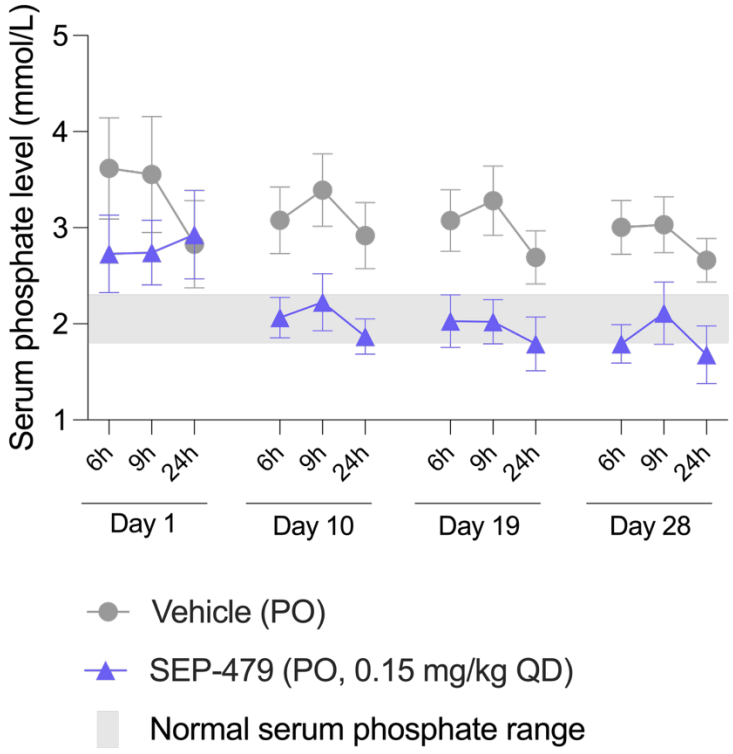
Normalize serum calcium

SEP-479: 28-day Oral QD Dosing

Sustained Normalization of Serum Ca^{2+} Levels



Sustained Normalization of Serum Phosphate Levels



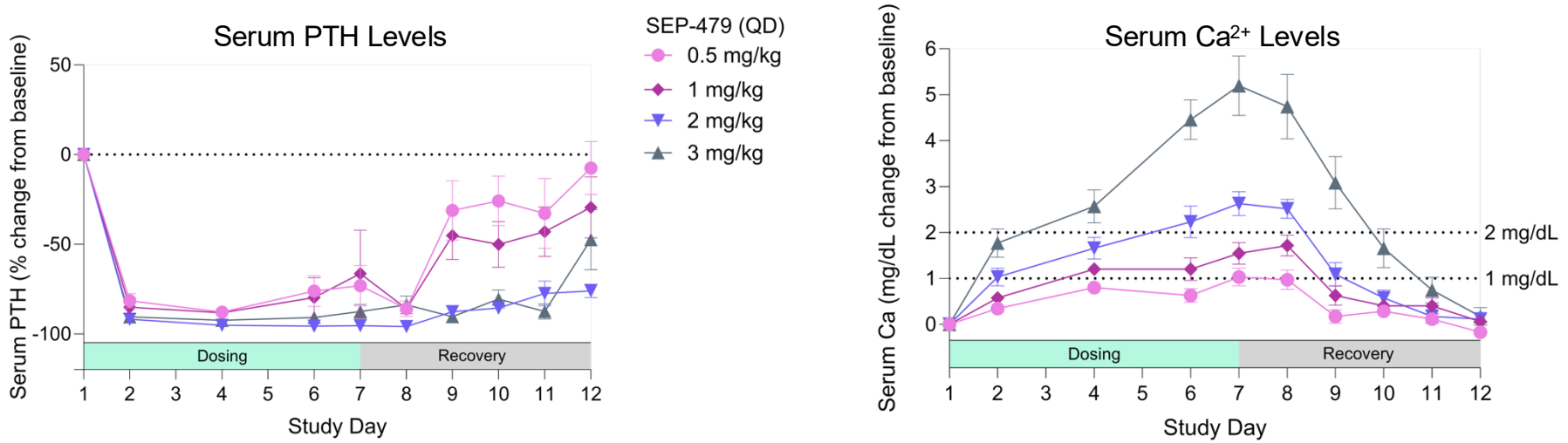
PO: oral dosing QD: once daily dosing BID: twice daily dosing

SEP-479 Lowered Endogenous PTH and Increased Serum Calcium In Healthy Cynomolgus Monkey Pharmacodynamic Study

In healthy animals (and humans) with normal parathyroid gland function:

- Treatment with PTH agonists leads to rapid suppression of endogenous PTH secretion to maintain normal calcium levels
- When feedback suppression of endogenous PTH reaches its limits, PTH agonist therapy at higher doses leads to calcium increases

SEP-479: 7-day Healthy Cynomolgus Monkey Pharmacodynamic Study



Lessons from PTH peptide clinical trials:

- Doses in healthy subjects that increase calcium ~0.5-1 mg/dL translated to relevant therapeutic pharmacology in hypoparathyroidism patients

SEP-479 Preclinical Profile Supported Advancement into Phase 1

Potent oral small molecule PTH1R agonist

- Demonstrated effects comparable to PTH peptides in cell-based assays and in vivo models

Pharmacokinetic studies

- Demonstrated high oral bioavailability and long half-life following oral dosing across preclinical species (mouse, rat, dog, cyno)
- Projected human half-life is approximately 40-80 hours with potential to support QD human dosing

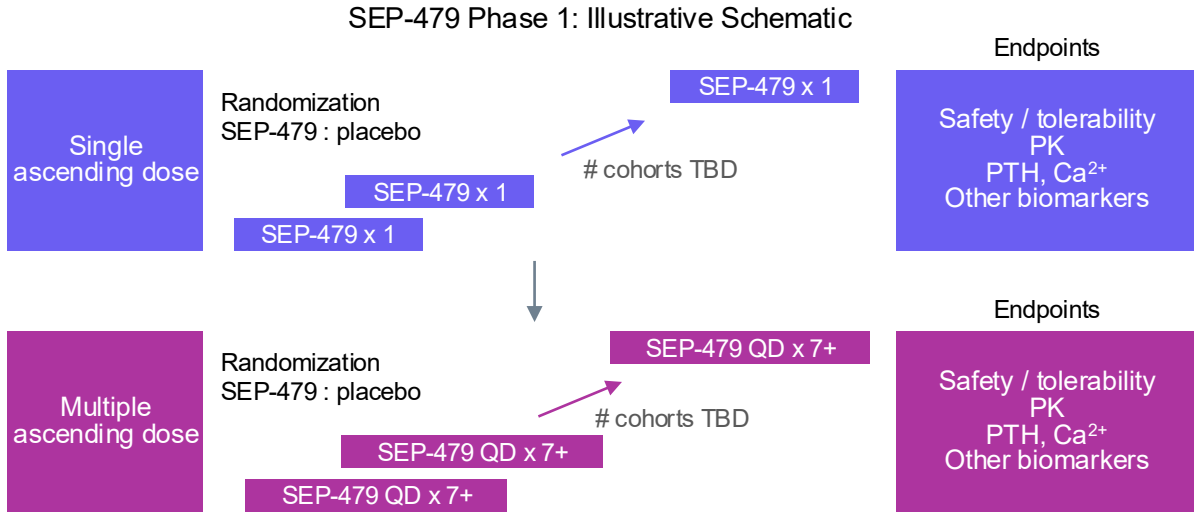
Non-clinical safety studies

- Generally well tolerated in three non-clinical safety studies (28-day GLP toxicology in rats, dogs, cyno)
- Dose-limiting effect in each species was on-target hypercalcemia, as expected for a PTH1R agonist

SEP-479 Phase 1 Study in Healthy Volunteers is in Progress

Study design:

- Randomized, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) trial in healthy adult volunteers
- Will also include a cross-over food effect study
- Estimated enrollment: up to ~150 subjects (in Australia)



Translation of healthy volunteer studies to hypoparathyroidism patients:

- Healthy subjects and hypoparathyroidism patients both have intact PTH1R in the bone and kidneys to control serum calcium
- Injectable PTH peptide trials: changes in serum calcium translated well from healthy volunteers to hypoparathyroidism patients

Objectives for SEP-479 during dose escalation in healthy volunteers:

- On-target pharmacology to be confirmed initially with decreases in endogenous PTH, and at higher doses, with increases in serum calcium

Anticipate SEP-479 SAD / MAD results in late 2026 or early 2027

SEP-631: Oral Small Molecule MRGPRX2 NAM

Targeting MRGPRX2 for Mast Cell-Driven Diseases

MRGPRX2 is a Key Regulator of Mast Cell Degranulation Activated by Several Endogenous Ligands

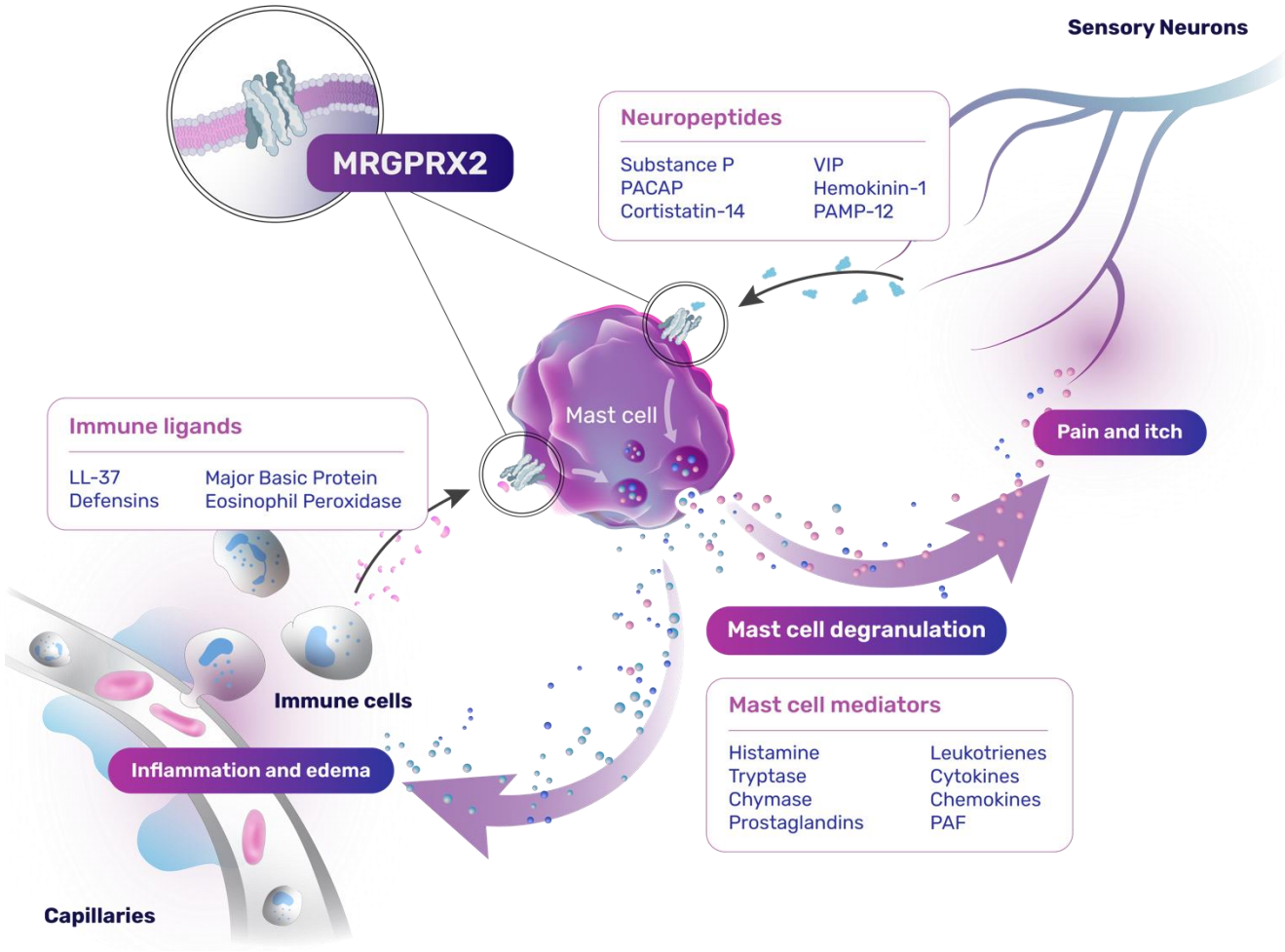
MRGPRX2 is activated by a host of endogenous agonists leading to IgE-independent mast cell degranulation

- Include several neuropeptides and immune ligands

Mast cell degranulation leads to release of mediators which cause pain, itch, inflammation, and edema

- Pain and itch are driven by mast cells co-localized with sensory neurons
- Inflammation and edema are driven by mast cell mediator effects on tissue capillaries leading to vasodilation, vascular permeability, and leukocyte recruitment

Targeting MRGPRX2 has the potential to disrupt feedback loops that drive these effects



SEP-631: MRGPRX2 NAM with a Potentially Differentiated Profile for Mast Cell-Driven Diseases

SEP-631 is a negative allosteric modulator (NAM)

- Binds to a novel allosteric site, distinct from the agonist binding pocket

Potently inhibits MRGPRX2 activation with an insurmountable NAM profile

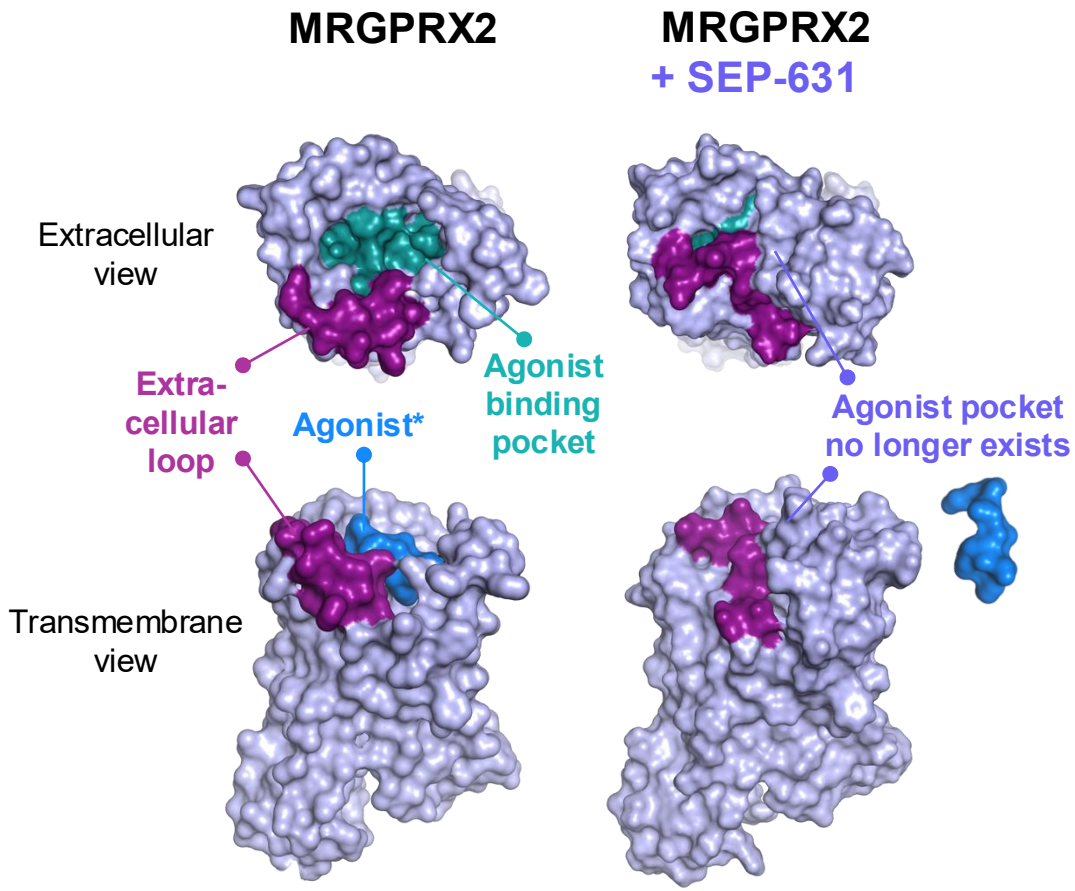
- Very high binding affinity (Ki ~0.5 nM)
- Slow dissociation rate ($t_{1/2}$ > 2 hours)

Locks MRGPRX2 in a state that prevents binding of all agonists, even at high agonist concentrations

- Potent inhibition of MRGPRX2-induced degranulation for both mast cell lines and primary human skin mast cells

PK profile across species projected to once-daily oral dosing in humans

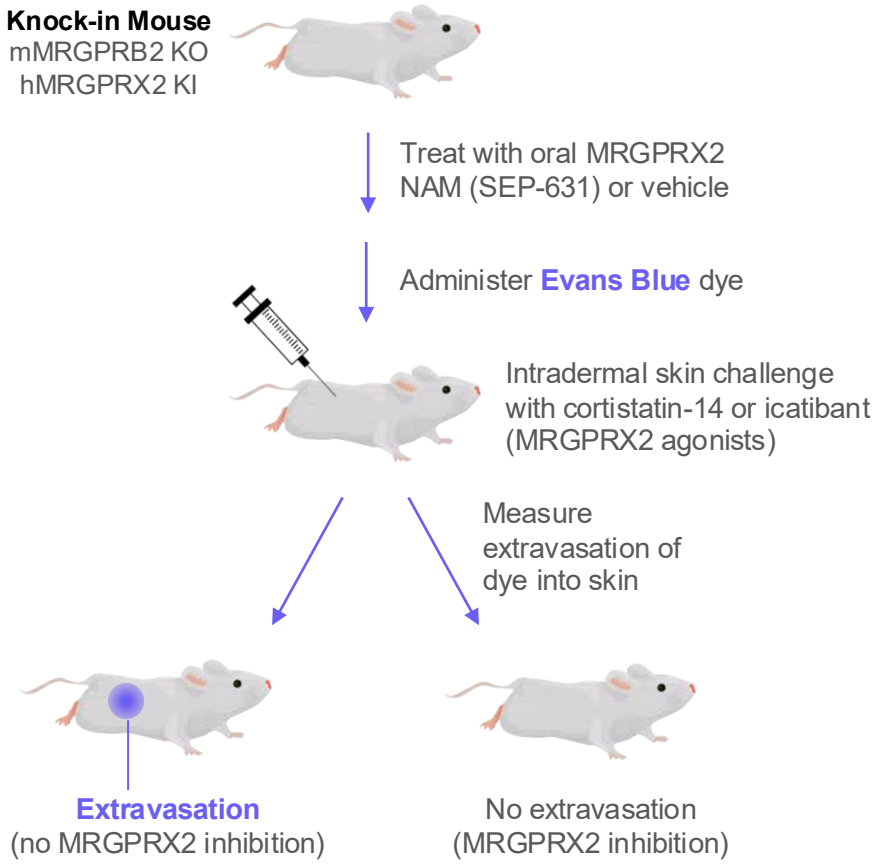
SEP-631 Induces a Structural Change in MRGPRX2 That Completely Closes the Agonist Binding Pocket



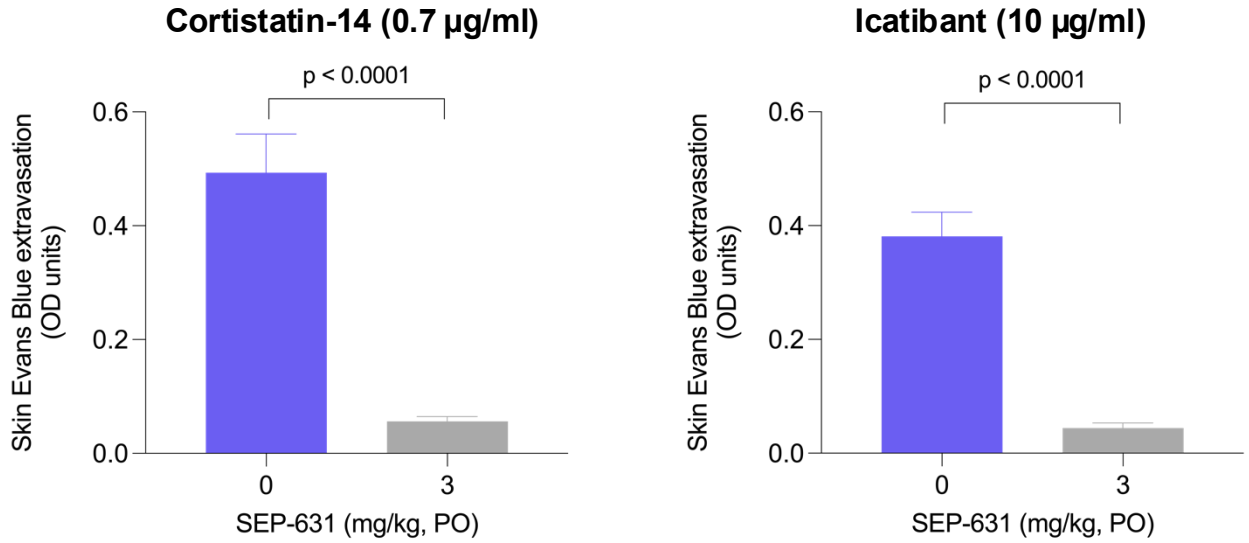
*Cortistatin-14

SEP-631 Inhibited MRGPRX2 Activation in Humanized Mouse Translational Model

Human MRGPRX2 Knock-in (KI) Mouse Model of Skin Extravasation



SEP-631 Potently Inhibited Skin Extravasation



SEP-631's insurmountable NAM profile translated to complete inhibition of MRGPRX2-mediated skin extravasation in a preclinical urticaria translational model

KO: gene knockout KI: gene knock-in

SEP-631 Preclinical Data Supports Potential Best-in-Class Profile

SEP-631 Preclinical Profile

- **Subnanomolar binding affinity and slow off-rate kinetics**
- **Insurmountable negative allosteric modulator mechanism closes off agonist binding pocket**
  - Inability to activate receptor despite presence of high doses of endogenous agonists
- **Potent inhibition of MRGPRX2 activation in knock-in animals and primary human mast cells**
- **Excellent oral PK across species**
  - Projects to once-daily human dosing
- **Excellent pharmaceutical properties**
  - Low drug-drug interaction risk based on in vitro profiling
  - Low food effect risk based on preclinical studies
- **Generally well-tolerated in pharmacology and GLP toxicology studies**
- **Convenient tablet formulation developed**

SEP-631 Phase 1 Study Design

Goal: Evaluate the safety, tolerability, PK, PD (with an icatibant skin challenge), and food effects

- 120 healthy adult volunteers, double-blind, randomized, and placebo-controlled SAD/MAD study design

Part A. SEP-631 PO single dose (SAD)

Single ascending dose
n=8 / cohort

Randomization 6:2
(SEP-631:placebo)

10 mg → 30 mg → 90 mg → 200 mg → 300 mg → 400 mg

Key endpoints
Safety / tolerability
PK

Part B. SEP-631 PO QD for 10 days (MAD)

Multiple ascending dose
n=16 / cohort

Randomization 12:4
(SEP-631:placebo)

10 mg → 30 mg → 90 mg → 200 mg

Key endpoints
Safety / tolerability
PK
PD: skin challenge

Part C. SEP-631 PO single dose crossover

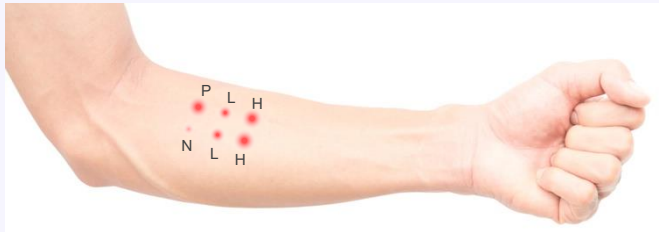
Food effect
n=8

Randomized open-label crossover

200 mg Fasted → 200 mg Fed
5-day washout
200 mg Fed → 200 mg Fasted

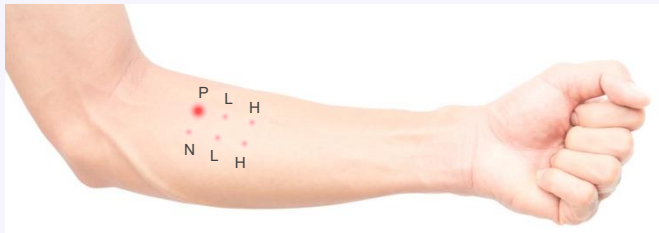
Key endpoints
Safety / tolerability
PK (fasted vs fed)

Skin Challenge (Pre-dose)



SEP-631 dosing
QD x 9 days

Skin Challenge Objective (Post-dose)



L = icatibant 10 µg/mL; H = icatibant 100 µg/mL;
N = negative control (saline); P = positive control (histamine)

SEP-631: Adverse Event Profile Comparable to Placebo and Pharmacokinetics Support Once-Daily Oral Dosing

Safety

- Rate of TEAEs with SEP-631 was comparable with placebo
- No severe or serious events were reported
- 3 events of mild transaminase elevations (<1.5x ULN) observed; not dose-dependent and comparable to placebo rates

Pharmacokinetics

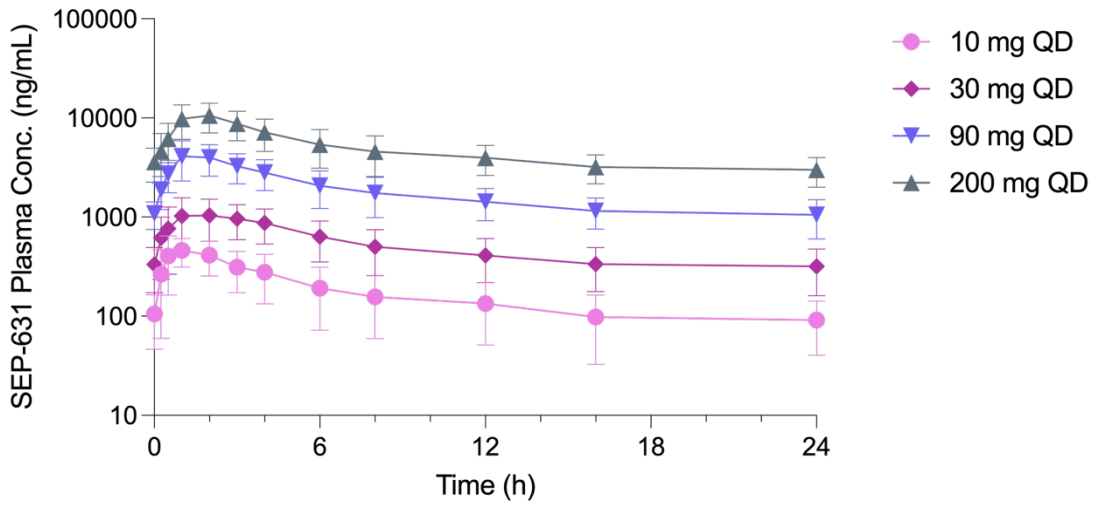
- Elimination half-life of SEP-631 is approximately 24 hours, supporting once-daily (QD) dosing

Food Effect Study

- SEP-631 with high-fat, high-calorie meal resulted in similar exposure to fasted conditions (AUC and Cmax)

SEP-631 was well tolerated with a PK profile that supports QD oral dosing and without food restrictions

Multiple Dose Pharmacokinetics (Day 10)



Pharmacodynamics Assessed Using an Icatibant Skin Challenge

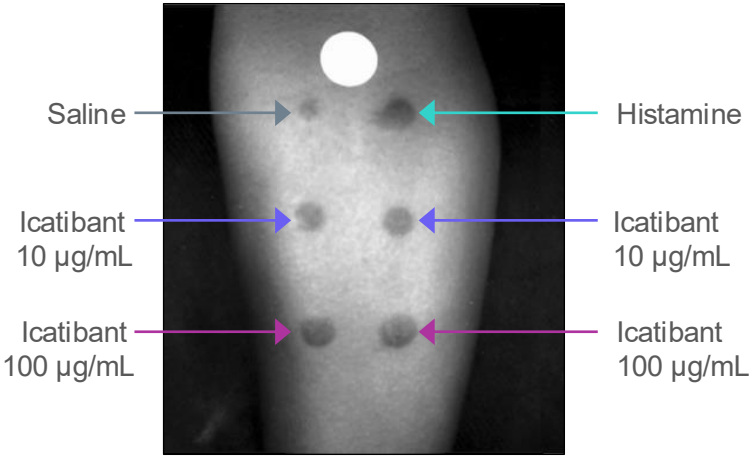
Icatibant is a selective MRGPRX2 agonist that induces a skin wheal response following intradermal injection

Skin challenge performed at baseline (Day –1) and steady-state (Day 9) following SEP-631 or placebo treatment

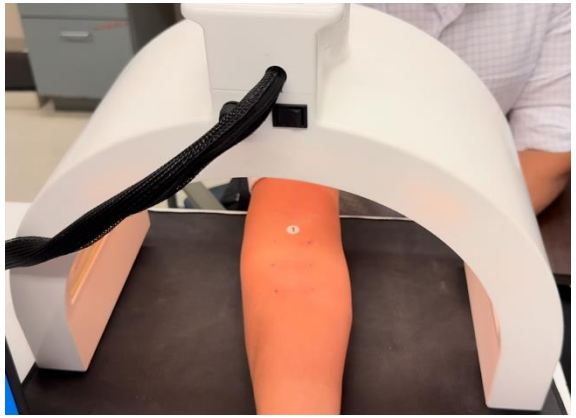
- Skin challenge agents: saline (injection negative control), histamine (wheal positive control), and icatibant at 10 µg/mL and 100 µg/mL

Wheals imaged using a precision image-based detector (AllergyScope™)

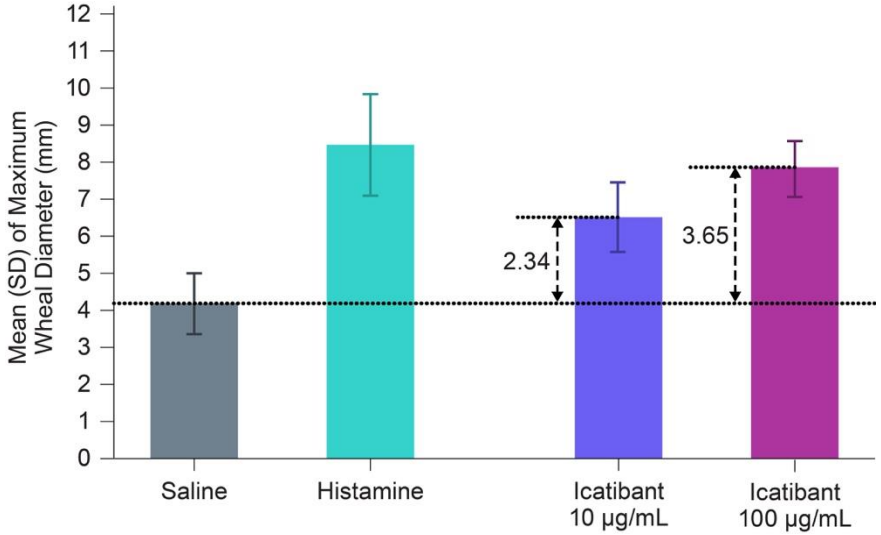
Forearm Intradermal Injection Pattern



AllergyScope™ Detector

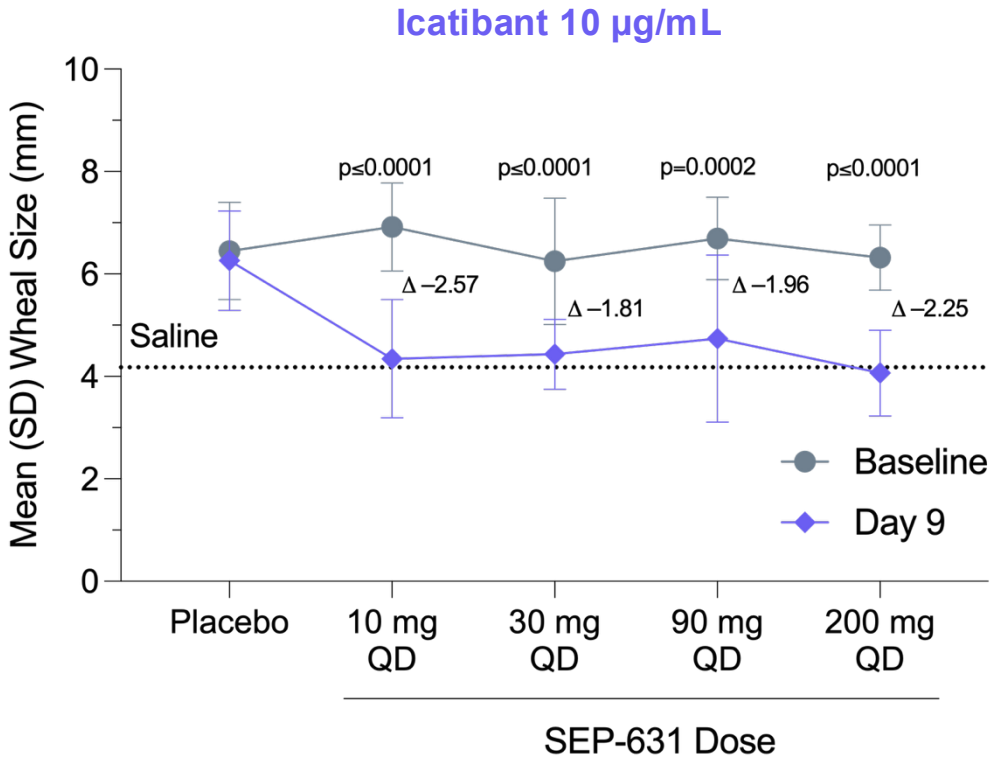


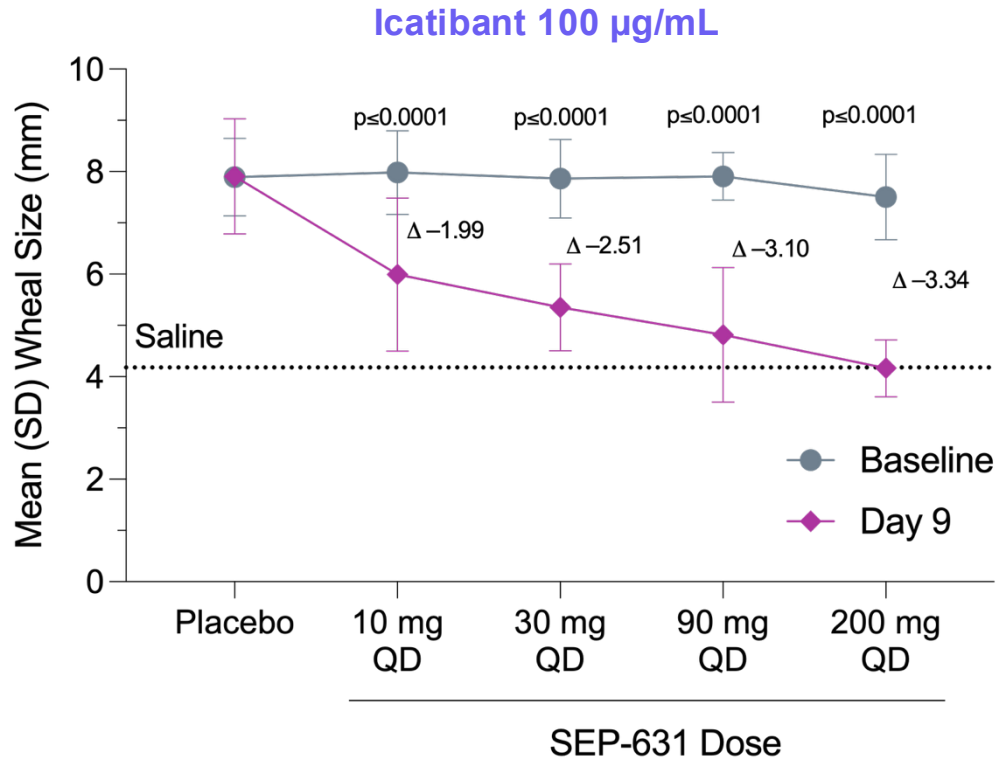
Baseline Skin Challenge (Day -1)



SEP-631 Inhibits Icatibant Wheal Formation in Dose-Dependent Manner to Complete Inhibition

- **SEP-631 completely inhibited icatibant 10 µg/mL-induced wheals at 10 mg QD, the lowest dose evaluated**
- **SEP-631 inhibited icatibant 100 µg/mL-induced wheals in a dose-dependent manner, with near to complete inhibition at 90 and 200 mg QD**





Nominal p-values comparing each SEP-631 dose level to placebo for change from baseline are based on an ANCOVA model including a fixed effect for treatment group and baseline wheal response as a covariate

SEP-631 Preclinical Profile Translated Well to Phase 1 Clinical Trial Results

SEP-631 Preclinical Profile	Translation →	Robust SEP-631 Phase 1 Results
• Subnanomolar binding affinity • Slow receptor off-rate kinetics	Target Coverage	• Estimated high receptor occupancy (>99%)
• Excellent oral PK across preclinical species	Pharmacokinetics	• Confirmed QD oral dosing (half-life ~24 hrs) • No food effect, excellent dosing flexibility
• Insurmountable NAM blocks agonist binding pocket for all MRGPRX2 agonists tested	Pharmacodynamics	• Full inhibition of icatibant-induced skin wheal formation at both high and low icatibant doses
• Generally well-tolerated in GLP tox studies • Low DDI risk based on in vitro profiling	Safety	• All AEs considered mild or moderate • No LFT abnormalities or other observations

Potential Best-in-Class Profile of SEP-631:

- Excellent potency with mechanism that provides broad insurmountable inhibition
- Clean clinical safety profile
- Convenient, once daily oral tablet with a flexible dosing schedule

SEP-631: Initial Phase 2 Development Strategy

Broad opportunity across a range of allergic and inflammatory diseases where mast cells are implicated in disease pathophysiology

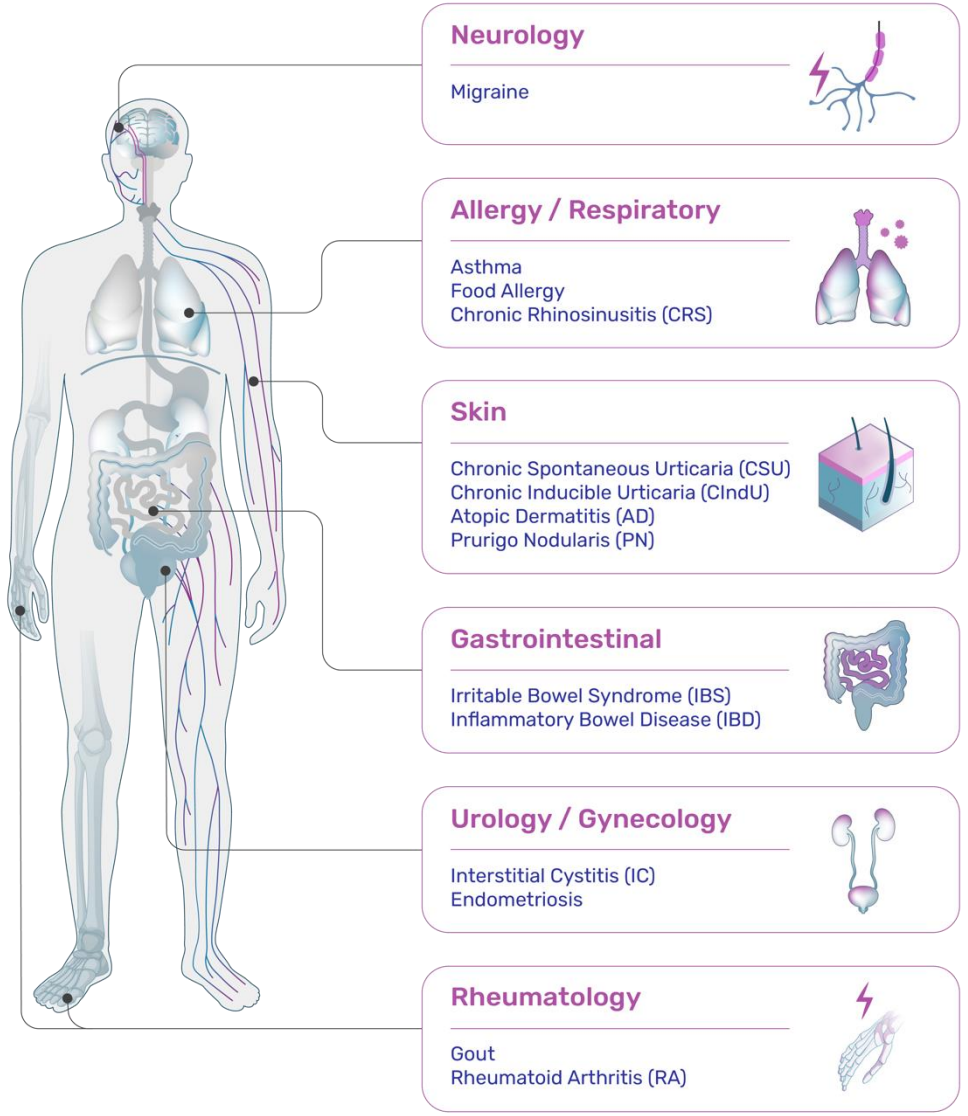
- Mast cells reside in organ systems throughout the body contributing to pain, itch, and inflammation

Our Strategy: since the skin has the highest level of MRGPRX2 expression on mast cells, plan to rapidly advance into Chronic Urticaria studies

- Targeting initiation of a Phase 2b Chronic Spontaneous Urticaria study in 2H 2026
- Pursue open-label Chronic Inducible Urticaria (CIndU) study in symptomatic dermatographism following initiation of CSU study

Exploring path forward in other high potential indications where tissue mast cells express MRGPRX2 including:

- Atopic Dermatitis, Interstitial Cystitis / Bladder Pain Syndrome, Migraine, and Asthma



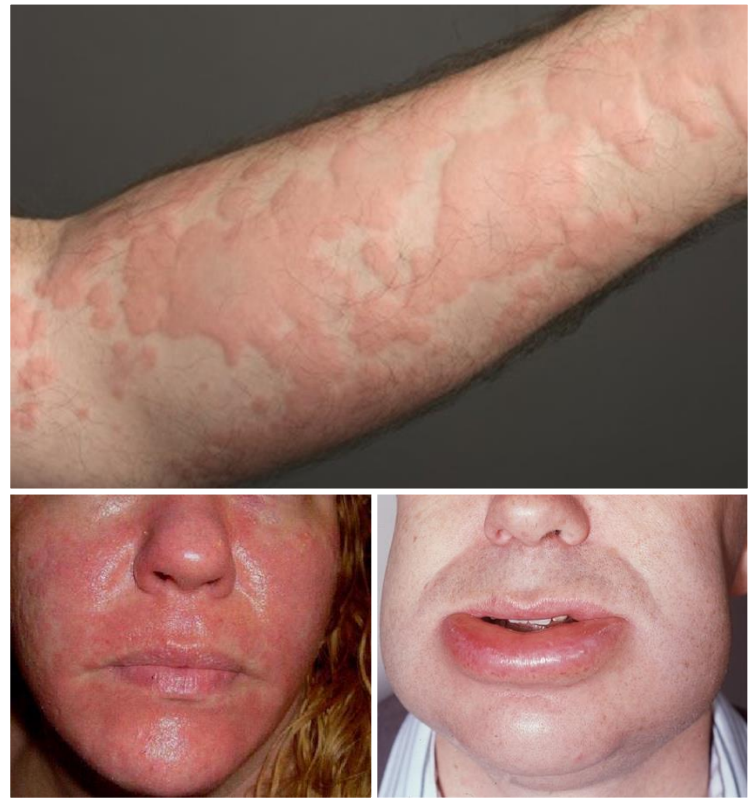
Chronic Spontaneous Urticaria (CSU): High Disease Burden, Large Patient Population

- **CSU is an undertreated dermatology condition characterized by itchy and painful wheals and angioedema**
- **Significant burden of disease; patients experience[1]:**

Disease Burden	% CSU Patients
High to very high impact on their daily life	~40%
Mod-to-severe pain / discomfort	~60%
Mod-to-severe anxiety / depression	~50%
Miss work at least once per week	~20%

- **~40% of patients are refractory to first-line high-dose antihistamines[2-4]**
- **High unmet need for safe second-line oral treatment options**
- **Growing commercial opportunity: ~2-3M CSU patients in the US[5]**

CSU Skin Wheals and Angioedema



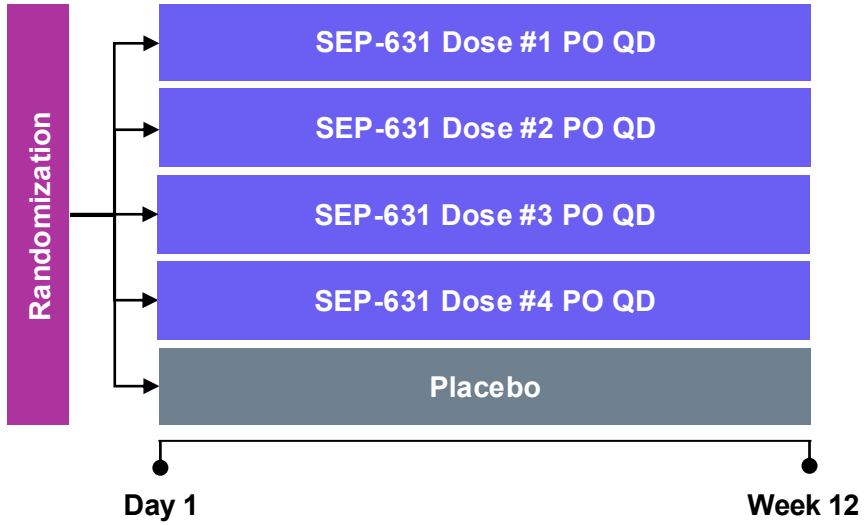
1. ASSURE study, 2. 2022 Kaplan, et al CSU Review article, 3. AWARE study, 4. Guillen et al., 5. GA²LEN task force report

Plan to Initiate Phase 2b Dose-Ranging Chronic Spontaneous Urticaria Study in 2H 2026

- **Long-term GLP toxicology studies in rats and dogs to be completed by mid-year 2026**
- **Planned global, randomized, double-blind, placebo-controlled study to evaluate safety and exploratory efficacy of SEP-631 in CSU**

Patient Population:

- Adults 18 to 65 years
- Moderate to Severe CSU
- Remain symptomatic on second-generation H1 antihistamine



Primary Endpoint:

- Change from baseline in UAS7 at Week 12

Key Secondary Endpoints:

- Safety / Tolerability
- UAS7≤6 and UAS7=0
- Change in ISS7
- Change in HSS7

- **Following initiation of the CSU study, we plan to pursue an open-label Chronic Inducible Urticaria (CIndU) study**

UAS7: Urticaria Activity Score over 7 days; ISS7: Itch Severity Score over 7 days; HSS7: Hives Severity Score over 7 days

Exploring Opportunities for SEP-631 in Additional Indications with High Unmet Need

- **Indications characterized by mast cells playing a central role in disease pathology and evidence of MRGPRX2 expression on tissue-resident mast cells**
- **Indications cover breadth of target organs and have different pathologies and unmet needs**
- **Developing cost-efficient and right-sized clinical strategies to demonstrate SEP-631 benefit**

Atopic Dermatitis

- >10M moderate to severe AD patients[1,2]
- MRGPRX2 could play a central role in itch resolution
- Safe, oral treatment would grow market

Interstitial Cystitis

- ~1-4M interstitial cystitis patients[3]
- No compelling treatment options
- Bladder has second highest level of MRGPRX2 expression after skin

Migraine

- ~15-25M moderate-to-severe migraine patients[4]; ~40% would benefit from preventative treatment[5]
- Current therapies provide only modest efficacy and drug cycling is common

Asthma

- ~1-3M severe asthma patients[6,7]
- High unmet need for safe, oral treatment

Estimates are US addressable patients. 1. National Eczema Association, 2. 2019 Fuxench, et al, 3. 2022 Anger, et al, 4. 2024 Cohen, et al, 5. 2021 American Headache Society Consensus Statement, 6. ACAAI, 7. 2020 Wang, et al

TSHR NAM Program

Oral Small Molecule Targeting TSHR for Graves' Disease and TED

No Disease-Modifying Therapies for Graves' Disease and Thyroid Eye Disease (TED)

Graves' Disease & TED Pathophysiology:

- Autoantibodies activate TSHR in thyroid gland and in orbital fibroblasts behind the eyes

Graves' Disease

- >2M patients in US
- Standard-of-care: antithyroid drugs, radioactive iodine, thyroidectomy

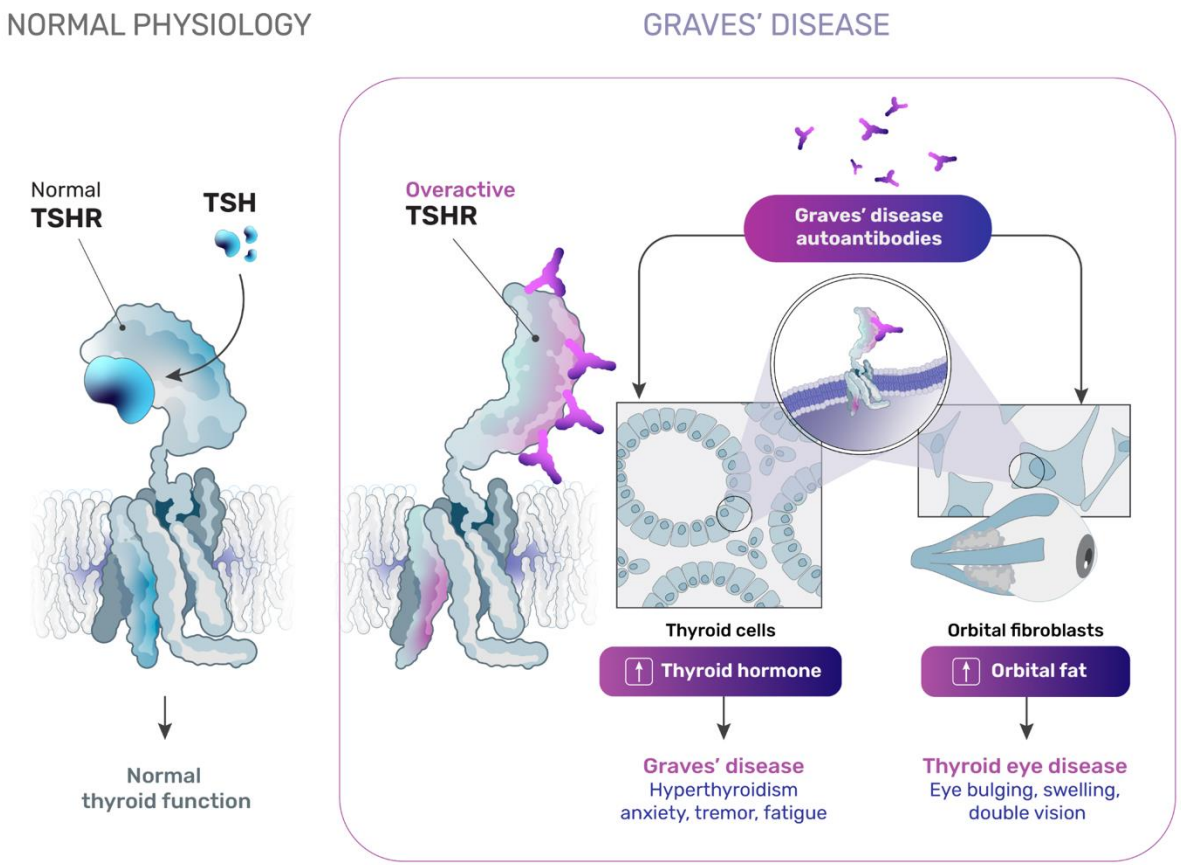
TED

- Develops in ~50% of Graves' disease patients
- TEPEZZA® (anti-IGF-1R) decreases proptosis but requires multiple IV infusions; serious side effects (e.g., hearing loss)

Challenge: Each Patient Has Unique Autoantibodies

- High-affinity, frequently polyclonal, high titer

Our Strategy: TSHR NAM as oral disease-modifying treatment for all Graves' disease and TED patients



Oral Small Molecule TSHR NAMs Reversed Symptoms in Novel Graves' Disease Model

- **Selective TSHR NAMs**
  - Blocked activation of TSHR by patient-derived autoantibodies
  - Insurmountable NAM profiles in cell-based assays
- **Preclinical Leads Inhibited Diverse Patient Autoantibodies**
  - Fully inhibited several Graves' patient polyclonal serum samples in primary orbital fibroblasts
- **Reversed Graves' Animal Disease Model Effects**
  - Normalization of thyroid hormone T4
  - Reduction in thyroid weight
  - Reversal of proptosis

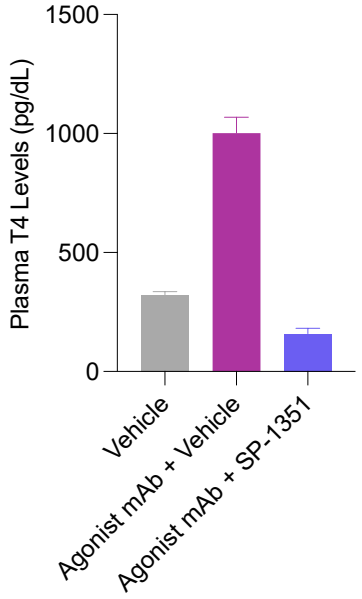
Mouse

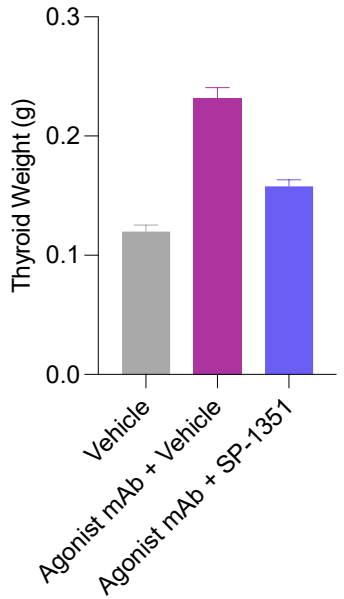
TSHR Activating Antibody → 6 weeks

↑ Thyroid Hormone Levels
↑ Thyroid Size
↑ Eye Proptosis (bulging)

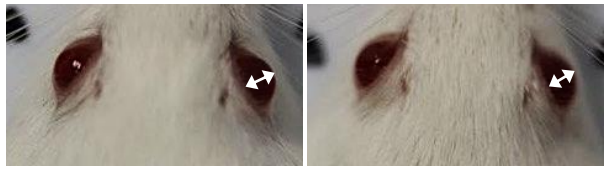
TSHR Activating Ab +TSHR NAM → 1 week

Reversal of Thyroid and Eye Manifestations

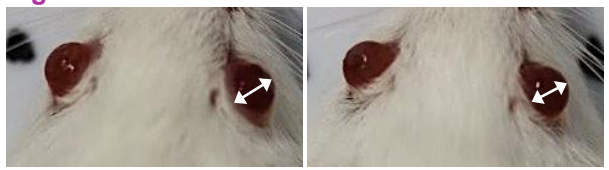




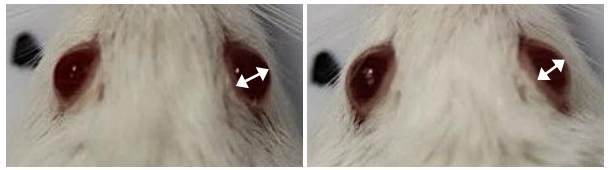
Isotype mAb control + Vehicle



Agonist mAb + Vehicle



Agonist mAb + SP-1351



Lead optimization is ongoing towards selection of a development candidate

Metabolic Programs

Oral Small Molecule Programs Targeting GLP-1R, GIPR, GCGR and Other Targets for Obesity, Diabetes, and Other Cardiometabolic Diseases

Collaboration with Novo Nordisk for Oral Small Molecules for Metabolic Diseases

Septerna and Novo commenced four initial R&D programs targeting five GPCRs

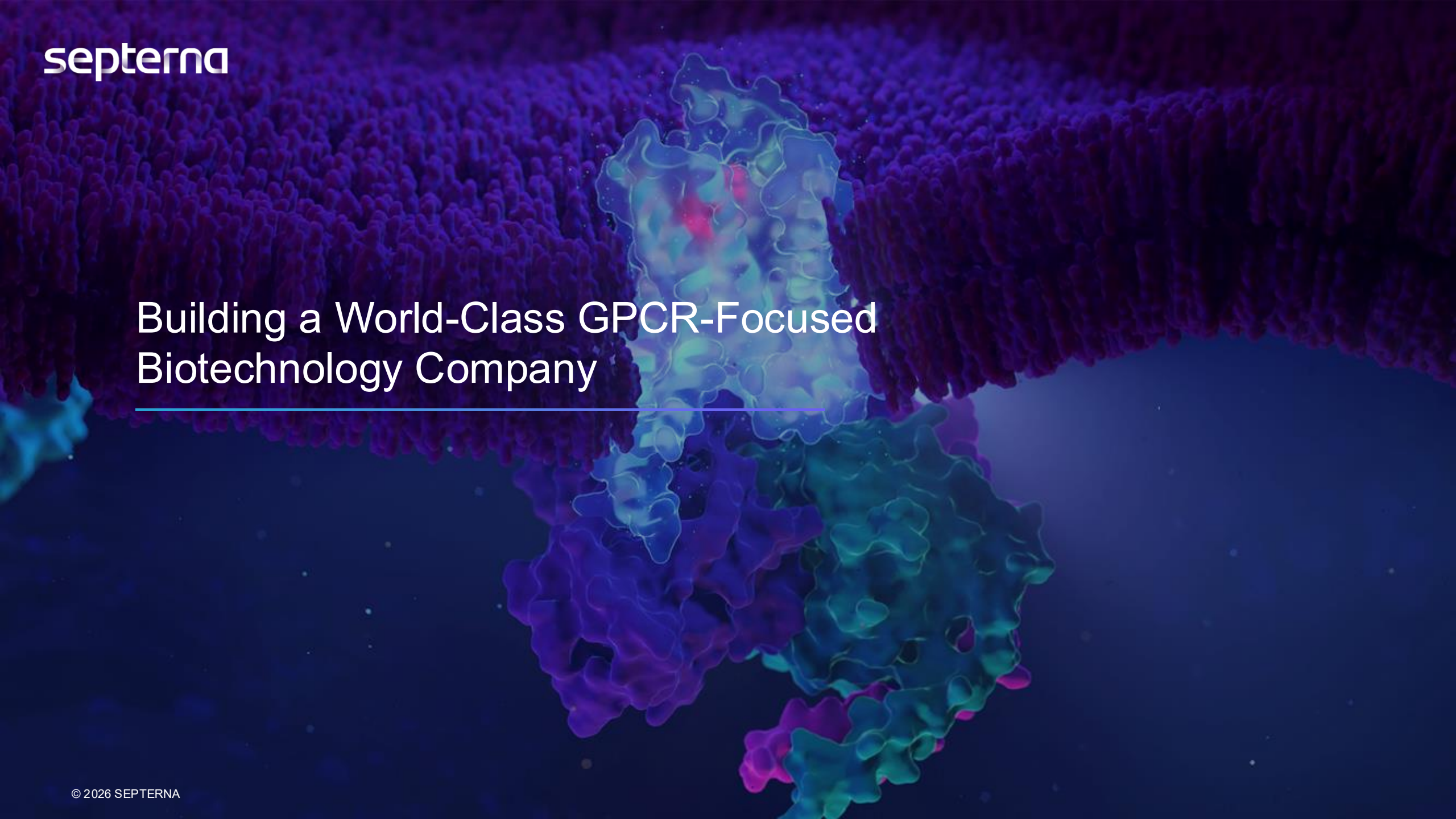
- Includes GLP-1, GIP and glucagon receptors
- Collaboration includes Septerna's preclinical, selective, oral, small molecule GIP receptor agonists

Potential multi-billion $ opportunity

- $195M upfront payment received in July '25
- ~$500M in R&D, regulatory and commercial milestones for each program
- Mid-to-high single-digit tiered royalties based on global product sales
- Opt-in right for worldwide profit-share for one program

Novo responsible for coverage of all collaboration R&D expenses

Collaboration Objective: discover, develop and commercialize multiple novel mono-, dual-, or triple-acting oral small molecule drug candidates directed to obesity, type 2 diabetes and other cardiometabolic diseases



Building a World-Class GPCR-Focused Biotechnology Company

Proven Leaders in GPCR Drug Development and Company Building

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CMO


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CFO


Uwe Klein, PhD
SVP Biological Sciences


Dan Long, DPhil
SVP Drug Discovery


Samira Shaikhly
CPO


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Septerna: Pioneering a New Era of GPCR Drug Discovery

- **Portfolio of oral small molecule GPCR-targeted programs**
- **Multi-product pipeline, each with a multi-billion $ market opportunity**
- **Native Complex Platform® drives rapid compound identification and portfolio expansion**
- **Well-capitalized with cash runway expected to support operating plans at least into 2029**

Wholly-Owned Programs	Development Status			
Program / Target Mode of Action	Discovery	IND-enabling	Phase 1	Phase 2
SEP-479 (PTH1R) Agonist				Anticipate Phase 1 data in late 2026 or early 2027
SEP-631 (MRGPRX2) Negative Allosteric Modulator				Phase 2 initiation* anticipated in 2H 2026
TSHR Program Negative Allosteric Modulator				

Partnered Programs		Partner
Metabolic Programs GLP-1R, GIPR, GCGR + Undisclosed	Obesity and Other Cardiometabolic Diseases	novo nordisk®
Undisclosed	Undisclosed	VERTEX

* Pending successful completion of regulatory submissions

Pioneering a New Era of GPCR Drug Discovery

Appendix

Safety: Single Dose Adverse Event Profile Comparable to Placebo

- **Rate of TEAEs with SEP-631 was comparable with placebo**
- **No severe or serious events were reported**
- **2 AEs of mild transaminase elevations (<1.5x ULN) observed with SEP-631 were not related to dose, and at rates comparable to placebo**

	Pooled placebo (n=12)	SEP-631 Single Dose						
		10 mg (n=6)	30 mg (n=6)	90 mg (n=6)	200 mg (n=6)	300 mg (n=6)	400 mg (n=6)	Pooled SEP-631 (n=36)
Any TEAEs, n (%)	5 (41.7)	2 (33.3)	4 (66.7)	0	4 (66.7)	3 (50.0)	1 (16.7)	14 (38.9)
Mild	5 (41.7)	2 (33.3)	3 (50.0)	0	4 (66.7)	2 (33.3)	1 (16.7)	12 (33.3)
Moderate	0	0	1 (16.7)	0	0	1 (16.7)	0	2 (5.6)
Severe	0	0	0	0	0	0	0	0
Serious TEAEs, n (%)	0	0	0	0	0	0	0	0
TEAEs in >1 subject, n (%):								
Headache	1 (8.3)	0	2 (33.3)	0	1 (16.7)	1 (16.7)	0	4 (11.1)
Transaminases increased	1 (8.3)	1 (16.7)	1 (16.7)	0	0	0	0	2 (5.6)
Dysmenorrhoea	0	0	1 (16.7)	0	0	1 (16.7)	0	2 (5.6)

TEAE, treatment-emergent adverse event as number (%)

Safety: Multiple Dose Adverse Event Profile Comparable to Placebo

- **Rate of TEAEs with SEP-631 was comparable with placebo.**
- **No severe or serious events were reported**
- **One mild transaminase elevation (<1.5x ULN) observed with SEP-631 and one observed with placebo**

	Pooled placebo (n=15)	SEP-631 Multiple Dose (10 Days)				
		10 mg (n=12)	30 mg (n=12)	90 mg (n=12)	200 mg (n=12)	Pooled SEP-631 (n=48)
Any TEAEs, n (%)	10 (62.5)	3 (25.0)	6 (50.0)	5 (41.7)	4 (33.3)	18 (37.5)
Mild	10 (62.5)	3 (25.0)	6 (50.0)	4 (33.3)	4 (33.3)	17 (35.4)
Moderate	0	0	0	1 (8.3)	0	1 (2.1)
Severe	0	0	0	0	0	0
Serious TEAEs, n (%)	0	0	0	0	0	0
TEAEs in >1 subject, n (%):						
Headache	4 (25.0)	0	2 (16.7)	2 (16.7)	1 (8.3)	5 (10.4)
Dizziness	1 (6.3)	0	0	2 (16.7)	1 (8.3)	3 (6.3)
Abdominal pain	0	2 (16.7)	0	1 (8.3)	0	3 (6.3)
Nausea	1 (6.3)	0	0	1 (8.3)	1 (8.3)	2 (4.2)
Fatigue	1 (6.3)	0	0	1 (8.3)	0	1 (2.1)
Dermatitis contact	1 (6.3)	0	1 (8.3)	0	0	1 (2.1)
ALT or Transaminases increased	1 (6.3)	0	0	0	1 (8.3)	1 (2.1)
Dysmenorrhea	1 (6.3)	0	1 (8.3)	0	0	1 (2.1)

TEAE, treatment-emergent adverse event as number (%)

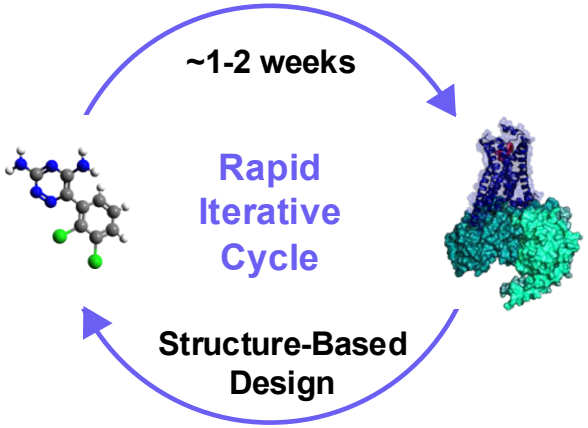
Native Complex Platform® is a Highly Efficient Platform for GPCR Structure-Based Drug Design

GPCR cryo-EM now achieving resolutions relevant for structure-based drug design

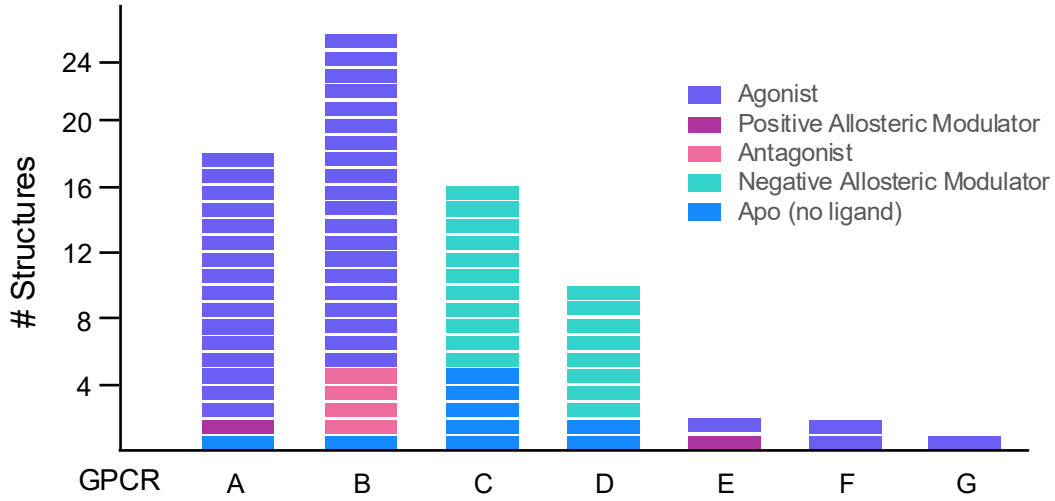
Native Complex cryo-EM enables rapid and iterative lead optimization

- Applies to a broad range of lead candidate modes of action (e.g., agonists, antagonists, allosteric modulators)
- >150 high-resolution cryo-EM structures determined to date, fueling our drug discovery programs

Native Complex Cryo-EM



Native Complex High-Resolution GPCR Structures



cryo-EM = cryogenic electron microscopy

SEP-786: First Clinical PTH1R Agonist Discontinued in Phase 1 in February 2025 Due to Unanticipated Events

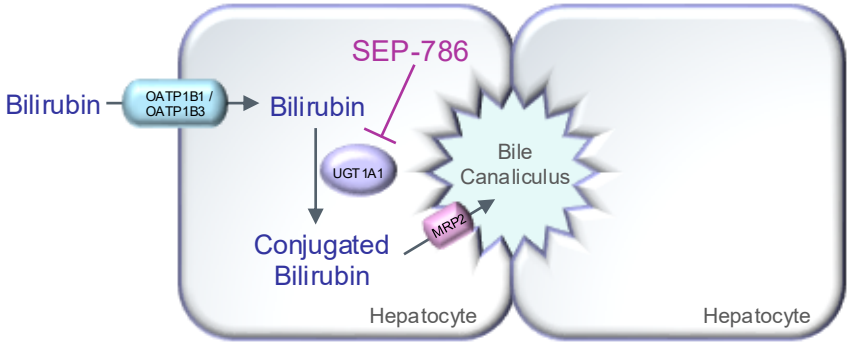
SEP-786 Phase 1 SAD/MAD trial in healthy volunteers discontinued

- 2 unanticipated severe (Grade 3) events of elevated unconjugated bilirubin levels in MAD
- Both events were reversible and without liver injury (normal AST, ALT, GGT), cholestasis, or hemolysis
- Not predicted by preclinical studies including 28-day GLP toxicology studies in rats and dogs

Early signals of on-target pharmacology seen for SEP-786 prior to trial discontinuation

- Observed initial increases in serum calcium and decreases in endogenous PTH (as anticipated for healthy subjects)
- Observed human half-life of ~18 hours would have likely supported QD or BID oral dosing

Investigation into the mechanism of unconjugated hyperbilirubinemia



Post Clinical Discontinuation Findings:

- SEP-786 is a potent UGT1A1 inhibitor* which is a known mechanism for increases in unconjugated bilirubin
- In a cynomolgus monkey study with SEP-786 (conducted after clinical discontinuation), elevated unconjugated bilirubin was observed

*Note: UGT1A1 is not routinely tested if glucuronidation is not the major drug metabolism pathway